REMARKS

Claims 1-21, 43-46 and 48-65 are pending. Claims 1, 2, 8, 13, 17-21, 45, 46 and 51-62 have been amended to consistently refer to α-1,3-galactosyltransferase or α-GT genes. No new matter has been added. Applicants reserve the right to prosecute any withdrawn or cancelled subject matter in one or more continuation or divisional applications.

We were very pleased to note that the Examiner indicated that claims 19-21 are allowable if rewritten in independent form. However, the Examiner continues to reject the remaining claims as anticipated under 35 U.S.C. §102(a) or rendered obvious under 35 U.S.C. §103(a).

Rejection under 35 U.S.C. §102(e)

The Examiner has rejected claims 1-8, 13, 17-18, 43, 48, 60 and 62 under 35 USC §102(e) as anticipated by Hawley et al (US 2006/0242722A1). The Examiner states that the priority date of Hawley predates the priority date of the instant application and that Hawley teaches the production of piglets using cell clones lacking wild type α-1,3-galactosyltransferase (αGT) and that Hawley is not required to show actual reduction to practice in the priority document in order to predate the priority date of the instant application.

The Applicants respectfully note that both conception and reduction to practice of the present invention was completed prior to Hawley's provisional filing date. Applicants direct the Examiner's attention to New Scientist, "Mini-Pig Clone Raises Transplant Hope", January 13, 2003, provided with the May 16, 2008 response in this case. In this article, it is noted that the pigs of the present invention were born in July, 2002, prior to both the birth of the pigs described in Hawley and, more importantly, prior to the Hawley priority application. Additional evidence showing that the present invention was completed prior to the Hawley priority date is shown in the enclosed Press Release from PPL Therapeutics, Inc., entitled "World's First Cloned Double Knock-Out Pigs Lack Both Copies of Gene Involved in Hyperacute Rejection in Humans" and dated August, 2002. The Applicants therefore respectfully submit that conception and actual reduction to practice of the invention was completed prior to Hawley's priority date and respectfully request that this rejection under 102 (e) be withdrawn.

Rejection under 35 U.S.C. §103

The Examiner has also rejected claims 1-18, 44-46, 49-59, 61, and 63-65 under 35 U.S.C §103(a) over Lai et al. (*Science*, 295: 1089-1092, February 2002) in view of Straham, et al. (*Frontiers in Bioscience*, 1, e34-41, 1996). The Examiner concedes that Lai produced only heterozygous pigs, but asserts that Straham provides the motivation to breed homozygous knock out pigs because it indicates that the Gal-α-1,3-Gal (α-Gal) epitope was the major target for human anti-pig antibodies. The Examiner further states that because αGT null mice had been produced, it would not have been anticipated that this genetic modification would be lethal in the null animals.

Applicants do not dispute that the art recognized a need for αGT-negative swine to produce useful tissues for xenotransplantion. What Applicants dispute is that there was any expectation in the art that such animals would be viable. The Examiner has asserted that any such skepticism was overcome when it was shown αGT-negative *mice* were viable. However, as discussed below, at the time of filing there were well recognized differences in α-Gal epitope expression between mice and pigs, based on which one of ordinary skill in the art would have lacked any expectation that results obtained in mice could be applied to pigs. Applicants submit that none of the cited references overcome the documented skepticism in the art that an αGT-negative pig would be viable and thus none of the references, alone or in combination, render the present invention obvious.

The Applicants respectfully submit that one of ordinary skill in the art, prior to the present invention, would not have expected that αGT-negative swine would be viable, as discussed below, and the viability of α-GT-null mice would not have changed this expectation. In particular, one of ordinary skill would have been aware that α-Gal epitope expression differed dramatically between pigs and mice. As described in Tanemura and Galili ("Differential Expression of α-Gal Epitopes on Pig and Mouse Organs." *Transplantation Proceedings*. 32:843. 2000. attached), pig organs express <u>*between 10 and 500 times*</u> the α-Gal levels of mice organs. Tanemura and Galili note that,

> The observed extensive expression of α-gal epitopes in pig organs raises the possibility that this epitope may have certain biological roles in pigs (eg, in cell-cell interaction, or tissue organization in the course of

> development). If this assumption is correct, then pigs may not be able to develop in the absence of α-gal epitopes.

Similarly, Galili (Galili, U. (2001) *Biochimie* 83:557-563) notes that the abundant expression of α-Gal in pigs throws doubt onto whether a homozygous αGT-negative animal would survive.

As the Applicants have noted previously, the production of viable pigs lacking α-Gal would have been considered merely a wished for result prior to the present invention because the lack of α-Gal, normally present on the surface of *all* pig cells, would have been expected to be lethal. As noted in Galili, "Even if one succeeds in generating heterozygote pigs in which one of the two α1,3GT genes is disrupted, it is not clear at present whether a homozygous pig with two disrupted α1,3GT genes can develop." (see page 560). In addition, Galili notes that the difference between mice and pigs, and indeed between pigs and *all other animals*, casts doubt as to whether viability of any other low-Gal animal could be applied to pigs. Galili states,

> That the α-gal epitope is not an essential epitope in most mammals is implied from the 'natural' knock-out of this gene in primate evolution and from the recent successful knock-out in mice. We have recently found, however, that the expression of α-gal epitopes in pig kidney is 500- to 1000-fold higher than in mouse kidney. Also in other organs such as heart, lung, or liver, expression of α-gal epitopes is many fold higher in the pig than in the mouse. *This raises the concern that the abundantly expressed α-gal epitope may have some biological roles in pig development, such as in cell-cell interaction.* If this assumption is correct, pigs may not develop in the absence of this epitope. (emphasis added)

These references support that skilled artisans lacked an expectation that any αGT-negative pig would be viable, even after the development of αGT-null mice. We have also previously presented numerous additional references that support the high level of skepticism surrounding the production of viable pigs lacking α-Gal expression that existed prior to the Applicants' invention. For example, Ayares et al. (2001) *Graft* 4:80-85 note "[since] Gal epitope expression in pig organs is up to 500-fold higher than in mouse organs, there is the possibility that αGT activity is more crucial to the pig"; Sharma et al. (2003) *Transplantation* 75:430-436 note "it is possible that GT(-/-) pigs may not be viable because the GT gene is essential for embryonic development"; and Porter & Dallman (1997) *Transplantation* 64:1227-1235 note "[a]lthough

[αGT-negative mice] develop and remain fairly normal, the possibility exists that deletion of this enzyme could have more severe consequences in other animals".

In addition, this lack of expectation of success is supported by the lack of *actual* success found in the art. As the Examiner notes, Lai suggests that αGT negative animals would eliminate hyperacute rejection and permit long-term survival of transplanted porcine organs. However, prior to the present invention, attempts to produce such animals failed to achieve these goals. For example, Denning and colleagues attempted to produce αGT sheep and were unable to achieve any live births (Denning et al. (2001) *Nature Biotech* 19:559-562). Without an animal surviving for sufficient time to grow useful organs, no organs or tissues could be produced that could be used for xenotransplantation.

As the Examiner notes, the Applicants were not the first to believe that αGT animals would be desirable. Indeed, there was a long felt need for such animals, as showcased by the references cited by the Examiner as well as those noted above. What the Applicants *were* the first to do was to overcome the lack of expectation that such animals *could not be produced*. As noted above, not only was the art rife with statements noting that αGT-negative pigs would lack viability, but attempts to make such animals for xenotransplantation had failed prior to the Applicants' invention. As the Examiner is aware, prior art references can only be combined if there is an expectation that the combination will be successful in producing the claimed subject matter. The Applicants have provided substantial evidence to show that one of ordinary skill would not have expected *any* combination of the references cited by the Examiner to produce viable pigs lacking functional expression of αGT, as presently claimed. Only with the Applicants' present invention did the hope for viable pigs lacking functional α-Gal become a reality. Applicants respectfully request withdrawal of this rejection.

Applicants believe no additional fees are required with this response. Should the Examiner determine otherwise, the Commissioner is authorized to charge any underpayment of fees to Deposit Account No. 11-0980.

Respectfully submitted,

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